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14. ABSTRACT

Breast Cancer remains a leading cause of death for women in the US despite the popularity of mammography as a preventive tool. At diagnosis, many breast cancers are at an advanced stage of disease, even for women undergoing annual screening, resulting in costly and painful follow-up procedures. It has been shown that molecular markers can increase our ability to diagnose early stages tumors. This has been demonstrated by current clinical practices using the CA-125 marker and PSA for the detection of ovarian and prostate cancer, respectively. The purpose of this study is to search for breast cancer biomarkers and evaluate their effectiveness in detecting early stage carcinoma. By combining molecular diagnosis with current imaging analysis of breast tissue, we may further reduce the number of deaths as well as the number of women undergoing surgery due to breast cancer. To date, we have created the infrastructure necessary for our interdisciplinary team of investigators to obtain study samples from a well-characterized population, analyze candidate biomarkers, and efficiently communicate research findings. We are also exploring more efficient and sensitive biotechnology that may better assist our study investigators.

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Introduction

Although mammography significantly reduces its toll, breast cancer remains a leading cause of cancer mortality in the U.S. Many breast cancers are advanced at the time of diagnosis, even among women participating in screening. The discovery of molecular markers associated with breast cancer potentially increases our ability to diagnose early stage tumors. We are proposing that molecular diagnosis be combined with imaging to enhance our ability to identify breast cancer when it is most treatable, i.e. still localized to the breast. This study will test the hypothesis that use of a breast cancer serum biomarker panel can improve the performance of mammography in early detection of breast cancer. The primary aims of the study are: 1) to validate and refine the ability of candidate biomarkers measurable in blood products to predict disease status; 2) to evaluate panels of serum markers for use as an adjunct to mammography, to detect all breast cancer at a highly curable stage; and 3) to identify the molecular signatures of benign, pre-invasive and invasive breast tissue and explore their associations with serum markers in the panel.

We are focusing on markers that can be measured in serum, as they are generally inexpensive and not subjective in their interpretation. To avoid over-diagnosis, we will perform molecular profiling to identify aggressive subsets of breast cancer that are most likely to be missed by mammography and in need of early detection. Our current list of candidate markers includes circulating antibodies to oncogenic proteins known to be associated with aggressive disease such as Her2/neu, and IGFBP-2; and circulating tumor markers including growth factors associated with angiogenesis such as VEGF, DNA methylation markers, lipid markers, CD24, Psoriasin (S100 A7), Mammaglobin, and a panel of 10+ cytokines. At the end of this Center of Excellence study, the expected result is a panel of markers and decision rules for its use clinically to improve the performance of mammography.

Body

As previously reported, we began clinical recruitment activities in Seattle at Swedish Medical Center (SMC) in May, 2004. Since that time we have been actively recruiting women into the mammography and surgical cohorts (see tasks 1 and 3 respectively). For women receiving annual mammograms, we are using their mammography data (assessment codes, follow up recommendations, and breast density) in coordination with family history collected on our baseline questionnaire and the GAIL model to determine risk of breast cancer (high, elevated or average risk). The surgical cohort consists of women scheduled to undergo breast surgery for malignant or nonmalignant conditions. In July, 2005 we also received approval to begin surgical recruitment at Cedars-Sinai Medical Center in Los Angeles. Recruitment efforts at Cedars-Sinai are led by Drs. Beth and Scott Karlan. The clinical protocols for each site have been standardized as much as possible with shared data collection instruments and a web-enabled data entry system (Seattle Informatics Management System or SIM). Recruitment of women scheduled for breast biopsies at SMC was delayed while we waited to receive final human subjects approval from the Department of Defense. We were granted approval in December, 2006 and have been recruiting participants scheduled for biopsy since January, 2007. Once these participants donate a pre-biopsy specimen they are followed as part of the mammography cohort for the remainder of the study.

Our patient advocates continue to play an important role in our COE. Their activities during the past year include review of new participant materials, input into community outreach efforts such as our quarterly Women's Cancer Prevention and Detection Newsletter sent to women participating in the Women's Cancer Prevention and Detection Network and COE study, and participation in meetings that involve the review

and discussion of study progress. In the future, we envision that our COE patient advocates will work closely with COE investigators to help determine how best to use markers clinically.

Since 2005 we have held quarterly COE investigator meetings that included consumer advocate participation, as mentioned above, as well as staff involvement. Each meeting focuses on a topic relevant to the overall study: clinical impact and applications of biomarkers, biomarkers and laboratory developments, and informatics. The final meeting of the year is the Annual COE Workshop held in Seattle on the Fred Hutchinson Cancer Research Center (FHCRC) campus. All meetings include presentations by study investigators, collaborators and outside experts on work relevant to the aims of the COE with additional time allowed for discussion. Presentations in 2007 have focused on ways to collaborate with other investigators engaged in discovery work in an effort to increase our access to additional markers that may be good candidates for validation.

The 2006 COE Workshop was held last November (see Appendix A for meeting agenda). The 2007 COE investigator workshop will be held November 2nd and will focus on the findings from preliminary analyses of candidate markers using a Breast Discovery Set (BDS) composed of unblinded specimens donated by COE participants. Our guest speaker will be Dr. Toshi Taniguchi from Fred Hutchinson who will present on secondary mutations as a mechanism of acquired Cisplatin resistance in BRCA1/2 mutated cancers.

This year we have created standardized, regularly updated enrollment reports for the surgical cohort. These reports are available to investigators at FHCRC and Cedars-Sinai through the Computational Proteomics Analysis System (CPAS) website and will soon become accessible through SIM. Reports are also distributed at monthly investigator meetings and to physicians who assist in the recruitment of participants. Two example reports are attached as Appendix B. We are currently in the process of creating similar reports for the mammography cohort.

During the past funding period we have completed development of the Breast Mini-Triage Set (BMTS) that will be used to evaluate candidate markers for inclusion in a biomarker panel (see Task 10 for more details). The BMTS is blinded to preserve its utility for validation.

Clinical use of a marker panel is a complex area of study that requires integration of all of the information from marker analyses and molecular profiling as well as economic and health systems considerations. It is critical to understand what we want our biomarker panel to detect. The latter considerations are being studied through a micro simulation model that was initially developed through a previously funded DOD grant (DAMD17-94-J-4237). We are using the model to investigate the impact of DCIS detection and treatment on breast cancer mortality and associated over diagnosis. Specifically, the model is being used to generate disease histories, including disease onset, progression to diagnosis, and mortality, for a cohort of women in the United States. Mammography screening schedules are superimposed on these disease histories, allowing investigation of the efficacy of early detection of breast cancer, including the in situ stage. Cancer incidence data are combined with data from autopsy studies to estimate the prevalence of breast cancer, including DCIS, in the population. Model parameters are selected to replicate diagnosis patterns reported in published studies.

Using available data for breast cancer growth rates, mammography performance, and stage-specific survival, our analyses suggest that mammography use, including detection of DCIS at current rates, yields a 25% reduction in breast cancer mortality. We estimate that detection of DCIS accounts for over 20% of this reduction (5.6%), that 64%

of screen-detected DCIS would remain latent until death due to other causes (over-diagnosis), and that mammography detects only one fifth of the prevalent DCIS. These results are reported in a draft manuscript titled *Quantifying Risks of Breast Cancer Mortality and Overdiagnosis due to Mammography-diagnosed DCIS* that we continue to refine and expect to submit during the next funding period.

Below we outline each task included in our Statement of Work and detail efforts toward completion of each task. In October 2007, we applied for a no cost-extension extending this study for 12 additional months; therefore, this report represents our progress report for our 5th year of funding (months 49-60).

TASK 1: Recruit women undergoing mammography to donate serial blood samples (Mammography Cohort)

Task 1a: Obtain Consent to Contact and Screening Questionnaire from women undergoing mammography at participating facilities (months 22-60). This task is currently underway. Recruitment of potential participants occurs at Swedish Medical Center mammography clinics and community health and outreach events such as the Swedish SummeRun, which raises money and awareness for ovarian cancer research. To date, we have collected consent to contact from 1,978 women. These women were sent a short, one page screening questionnaire to collect preliminary risk information. 66% of the screening questionnaires have been returned. Information from these forms is entered into the SIM database and is used to select eligible women to approach for the COE study.

Task 1b: Obtain mammography data from participating facilities (month 22 and quarterly thereafter). Collection of mammography data is continuing. As reported previously we obtain periodic data downloads from Swedish Medical Center's Mammography Reporting System (MRS), an electronic database used by Swedish Medical Center radiology facilities. Our most recent download from March 2007 contained 475,177 mammography records from 123,454 patients. We anticipate receiving a new download by the end of October. For participants who receive mammograms outside of Swedish Medical Center we use self-reported information from the health status or baseline questionnaire to determine the location and date of the woman's most recent screening mammogram and contact the hospital or clinic directly to request a copy of the report and any subsequent diagnostic reports (if applicable.) The reports are then abstracted by trained study staff into the same data entry screens in SIM that store MRS data.

We run a linking algorithm to match study participants to their mammography results from MRS. Using this data we have been able to incorporate mammography information such as assessment code, density and follow-up recommendations into our risk algorithm. Approximately 80% of our participants have electronic records in the Mammography Reporting System.

In April 2008 Swedish Medical Center will switch from MRS to Epic, a new database system that will be used to store all future mammography data at their facility. In anticipation of this change we have arranged with Swedish personnel to obtain three downloads from MRS over the next 6 months, one in October, one in January, and a final one in March. This will provide us with enough updated data to continue study activities that utilize this information through the end of the next funding period. During this time we will also work closely with Swedish staff to set up a method for obtaining regular downloads of mammography data from the Epic platform.

Task 1c: Using on-going sampling technique, stratify population by risk (month 37 and quarterly thereafter). As reported above, we have collected consent to contact from 1,978 women and have received completed screening questionnaires from about 66%. If

determined eligible, women are sent a COE study invitation packet. To date, we have invited 1,322 women to participate in the study as part of the mammography cohort with 676 or 51% agreeing to participate.

Information collected on our study questionnaires and mammography results are used to stratify our study population by risk; that is, allowing us to characterize a woman as high, elevated or average risk. A woman is determined to be at high risk based on family history, if she is of Ashkenazi Jewish descent, self-reports a positive test for the BRCA 1 or BRCA 2 mutation, or has prior history of receiving a breast biopsy. A woman is determined to be at elevated risk for breast cancer by GAIL Model, breast density, mammography assessment codes, or mammography follow-up recommendations. The table below summaries the number of women enrolled into the mammography cohort and associated risk levels based on collected information.

Table 1. Mammography cohort participants classified by risk status

Risk Level	Participants	% of Enrolled
High Risk	220	33%
Elevated Risk	338	50%
Average Risk	118	17%

Task 1d: Approach selected women for blood donation (months 25-66). This task has been underway since October, 2004. Specimen collection from study participants has proceeded smoothly with the majority of blood donations occurring on or close to the date of the participant's annual mammogram. Of the 676 women enrolled in the COE mammography cohort, 73% or 491 women have completed their first blood donation. To date, 361 of these women have completed serial draws, and 72 have donated their final specimen and completed study participation.

Task 1e: Send blood donation appointment letters and epidemiologic risk factor questionnaires to consenting women (months 27-72). This task has been underway since December, 2004. To date, 491 women have completed one or more study blood draws. All of these women receive an epidemiologic risk factor (baseline) questionnaire and a shorter health status questionnaire at the time of their initial draw. The health status questionnaire is completed at the time of collection and provides an update on the woman's medical history and variables that might affect marker status. Of the women donating blood, 100% have completed and returned the health status questionnaire and 465 (95%) completed and returned the baseline questionnaire.

Participants are asked to donate blood and complete study questionnaires once a year for up to four years. The majority of women will complete a total of 3 blood collections although some may complete less or more depending on when they began participating in the study. At each follow-up appointment study participants are asked to complete another health status questionnaire to update any information that may have changed since their last collection.

In June 2007 we began conducting final blood draw appointments for all participants approaching their third or fourth collection. To collect updated family history information we created an end-of-study supplemental questionnaire (Appendix C.) This supplemental questionnaire is mailed to the participant with her final appointment confirmation letter. Women may choose to complete and mail back the questionnaire or bring it with them to their final appointment. To date 100% of the women who have completed a final blood collection also returned the supplemental questionnaire. All women who complete their final collection are sent a card thanking them for their participation in the study.

Task 1f: Receive and data enter questionnaires (months 26-76). As summarized above, 465 participants have completed baseline questionnaires and 491 have completed one or more health status questionnaires at the time of their initial and/or subsequent blood collections. Quality control data entry is performed on all baseline questionnaires and approximately 10% of the health status questionnaires. The database manager periodically reviews quality control data entry on all questionnaires to track our error rates and ensure quality control entry is occurring on a sufficient number of questionnaires.

TASK 2: Recruit women undergoing stereotactic biopsy to donate pre-biopsy and serial follow-up blood samples (Biopsy Cohort)

Task 2a: Finalize approach procedures to be used by Swedish Breast Care Center (completed). In September 2001, Dr. Urban received funds from an NCI-Avon "Progress for Patients" award (P5OCA83636) that allowed us to develop and test procedures to recruit and enroll women who were undergoing stereotactic biopsy at the Swedish Breast Care Center (SBCC), part of SMC. For this "Avon study" women were asked to provide a one-time, pre-biopsy blood donation and complete both the baseline and health status questionnaires. 139 women were enrolled in this study at SBCC. We are currently using the same procedures to recruit and enroll women scheduled for breast biopsies at SBCC into the COE study. Women enrolled into the COE are asked to give a blood sample prior to their biopsy procedure *in addition* to an annual sample at the time of subsequent mammograms.

Task 2b: Specimen Collection Specialist attends biopsy appointment to obtain informed consent, collect pre-biopsy blood sample, and provide epidemiologic risk factor questionnaire (months 38-72). In December, 2005 we revised our study protocol and materials in an effort to better accommodate patient flow at all participating biopsy facilities and help us to meet our recruitment goals for this population. In December, 2006 we received DOD human subjects approval of these modifications and began recruitment of this population in January, 2007. To date 13 participants have been enrolled, with 11 donating a blood sample just prior to their biopsy. A total of 9 participants have returned a baseline questionnaire. All participants completed a health status questionnaire.

Recruitment of this population has been slower than anticipated during the last 10 months. SBCC regulations stipulate that their staff must first approach potential participants about the study before we can contact them about participation. One of the recruitment challenges has been communicating with SBCC staff on a regular basis to ensure we are aware of all potential participants that have been approached about the study. In an effort to increase enrollment our collection staff plan to work very closely with SBCC personnel over the next year to make sure we do not miss opportunities to contact potential participants. Our staff will go to the SBCC 1-2 times per week to ask their staff about any patients that might be eligible for approach.

We also have access to a population of 139 women previously enrolled in the "Avon" study, a breast cancer research study NCI-Avon "Progress for Patients" award (P5OCA83636) funded as a supplemental grant to our ovarian SPORE Award. Participants in this study donated blood specimens at the time of biopsy using the same protocol currently employed for the COE. At the time of enrollment Avon study participants signed a consent form stating that their specimens and data could be used for future studies involving breast cancer and biomarker research. If necessary the blood

specimens from these women could be utilized for the Panel Development and Validation Sets in the COE.

TASK 3: Recruit women undergoing surgery to donate pre-surgery and follow-up blood samples, and collect tissue on selected breast cancer cases (Surgical cohort).

Task 3a: Work with surgeons' offices to integrate patient approach procedures into the patient care flow. (completed). We have worked closely with participating breast surgeons and clinic staff to design and implement patient approach procedures for recruitment that have proven to be successfully integrated with normal clinic flow. Currently we have 6 physicians who are referring patients to our study. Our study staff are able to maintain an open dialogue with participating physicians about study progress and procedures by checking in with them and their staff on a daily basis. This creates an environment where physicians and study staff are able to work together to continuously refine and improve our approach procedures.

Task 3b: Pilot patient approach and specimen collection procedures (completed).

Patient approach began in July, 2004. Following our approved protocol, Swedish Medical Center breast surgeons identify patients that are likely candidates for surgical specimen collection and at the pre-surgical visit approach these patients about study participation. If the patient is interested, the physician will obtain verbal consent for study staff to contact the patient either in person or by phone. If a study staff member is present at the clinic, the physician invites the woman to speak to the study representative who can help answer immediate questions or concerns. If the patient chooses, she may be enrolled at this time (if she meets the eligibility requirements). Otherwise, study staff contacts her by phone to discuss the study in further detail and set up an enrollment appointment to conduct in-person informed consent and collect a pre-surgical blood sample.

Task 3c: Routinely approach selected women undergoing surgery for blood and tissue collection or blood only collection (Months 24-72). This task is currently underway. To date, we have enrolled 344 participants in Seattle from SMC. Of these women, 85 (25%) have successfully completed questionnaire data and donated blood and tissue, and 189 (55%) have completed questionnaire data and donated only blood. 27 women have completed their final study appointment.

Task 4. Recruit women undergoing biopsy or surgery to donate a one-time only pre-surgical blood *and* tissue sample, as feasible, at Cedars Sinai Medical Center.

Task 4a: Finalize approach procedures to be used by Dr. Scott Karlan at Cedars-Sinai Medical Center (completed). This task has been completed and the Cedars-Sinai Clinical and Recruitment protocol received DoD Human Subjects approval in July 2005. Drs. Scott and Beth Karlan have approached physicians who attend Breast Center conferences, to educate them about available research protocols for interested patients. Recruitment flyers and brochures are posted around the Cedars Sinai campus (specifically, the Saul and Joyce Brandman Breast Center and the Cedars-Sinai Outpatient Surgery Center) and made available to raise patient awareness. This study is also listed on the Cedars-Sinai web site.

Eligible women previously scheduled for a breast surgical procedure that involves the removal of some or all of their breast tissue are approached about possible study participation. Patients are not scheduled for surgical procedures for the purpose of this

study alone. The Principal Investigator, co-investigators, or treating physicians (usually a breast surgeon, occasionaly a radiologist or a medical oncologist) help identify potential subjects. The treating physician makes initial contact with potential subjects and contacts a trained study staff member to consent the patient into the study if the woman agrees to participate.

Task 4b: Routinely approach selected women for blood and tissue collection (starting in month 37). In October 2005, Drs. Beth and Scott Karlan and their study staff began recruiting and enrolling eligible women into the COE study at Cedars Sinai Medical Center. Their study enrollment goal is 50 surgical women per year for the duration of the study. The population includes healthy women with no disease, women with benign lesions and pre-malignant breast diseases, and women with in-situ and invasive carcinoma. Since recruitment began the Cedars Team has successfully enrolled 129 women; 6 participants (5%) completed study questionnaires and donated both blood and tissue, 50 participants (39%) completed study questionnaires and donated blood only.

In an effort to increase the number of patients who complete study questionnaires, the Cedars Team has modified their procedures to include a follow-up call and follow-up mailing to all patients who do not return the study questionnaire after it is administered at enrollment. These new procedures will be implemented later this year.

Task 4c: Surgeon to collect healthy tissue, benign lesions, atypia, in situ disease, and invasive carcinoma tissue samples. (starting in month 37). The Cedars Sinai team has implemented the shared tissue collection protocol and has collected tissue samples from 120 study participants. Pathology information is centrally abstracted at FHCRC using a Patient Level Clinical Diagnosis form. Tissue review and characterization of collected sample(s) is shown below in Tables 3 and 4.

Immediately after the surgeon has removed the necessary tissue and the pathologist has taken what is required for pathologic diagnosis, a study Specimen Collection Specialist is permitted to collect specimens from the removed tissue for the purposes of the COE. All or part of the un-needed tissue is collected, labeled and processed for storage. The tissue is embedded in OCT and/or snap frozen. Tissue collected includes malignant tissue with adjacent normal tissue, as well as tissue from pre-malignant lesions and breast tissue from normal patients undergoing plastic surgery procedures at Cedars-Sinai.

The Patient Level Clinical Diagnosis form uses information that has been abstracted from pathology and other medical reports to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. A FHCRC study staff member completes this form for all COE surgical participants with the research nurse conducting quality assurance.

Breast Tissue Histology Review
Working closely with breast pathologists Drs Sean Thornton and Ellen Pizer of Washington Pathology Consultants, we have created a Breast Histology Tissue Review Form that we began using in 2007 to characterize all breast tissue samples. During the previous funding period we completed review of a pilot group of 60 tissues from 10 participants in an effort to discover whether the most severe diagnosis listed on the patient pathology report matched the actual histology of the tissue specimens collected. The results of this analysis are reported below in Tables 3 and 4. In summary, we found that tissue specimens must be independently reviewed to accurately determine histology; it is insufficient to rely solely on the pathology report from surgery. In follow-up analyses we also found that tissue histology varied among the multiple specimens collected from a single participant. Therefore in order to confirm the histology of each specimen histological review on that specimen must be performed.

We also use a Clinical Status Follow-Up Form to capture specific information regarding patient status after cancer diagnosis and surgery such as treatment, progression or recurrence of the primary cancer and any development of secondary cancers. This information is used to determine which blood and tissue samples are most appropriate for future molecular profiling and marker evaluation work.

Table 3. This table shows the % agreement between the most severe diagnosis reported in the patient's surgical pathology report and the tissue specimens collected from that surgery.

Agreement between tissue specimens collected from tumor site and most severe diagnosis from surgical pathology report	OCT (n =53)	Snap Frozen (n=36)	All Specimens (n=89)	Total percentage: all specimens
100% (specimen was composed entirely of the histology noted as the most severe diagnosis in the pathology report)	11	16	27	30.3%
50 - 99%	20	5	25	33.7%
1 - 49%	13	6	19	21.3%
0% (specimen did not contain the histology noted as most severe diagnosis in pathology report)	9	8	17	19.1%

Table 4. This table reports the percentage of tissue samples found to contain normal tissue collected from tissue adjacent to the tumor.

% of specimen collected from site adjacent to tumor that was found to contain normal tissue.	OCT (n=27)	Snap Frozen (n=14)	All Specimens (n=41)	Total percentage: all specimens
100% normal	13	8	21	51.2%
Between 50 - 99%	8	2	10	24.4%
Between 1 and 49%	1	0	1	2.4%
0% (specimen did not contain normal tissue)	5	4	9	22.0%

Task 5. Blood samples from Mammography and Surgical Cohorts are collected, processed into serum and plasma cryovials, and logged into specimen tracking system (months 26-74).

In all blood collections, the Specimen Collection Specialist collects up to 50 ml of whole blood. At the initial collection the phlebotomist will distribute the blood between 3 red top (serum) tubes, 1 purple top (EDTA plasma) tube, and one yellow top (ACD-plasma and lymphocytes) tube. For all subsequent draws, blood is collected in 4 red top tubes and 1 purple top tube.

Standard protocols are followed to process specimens into sera and plasma and aliquot them into cryovials uniquely labeled with study specimen ids. Specimens are then logged into the Specimen Tracking System database (STS).

The blood specimens are stored in 1 ml quantities to avoid damaging freeze-thaw cycles. Aliquoted specimens are entered into the specimen tracking system then transported to the study repository for long-term storage and will eventually be delivered to laboratory investigators for future analysis. Blood draw date and time, and time of processing and freezing are recorded in STS as well.

Task 6. Revise existing ovarian cancer database to accommodate breast tissue specimens and questionnaire

Task 6a: Analyze **current system** and prepare preliminary assessment of revised software design specifications (completed). As previously reported, FHCRC

programmers have enhanced an existing specimen tracking system (STS) to accommodate specimens and breast specimen data being collected as part of the COE. We currently track the following specimen data: date of blood and/or tissue donation, specimen processing, amount of specimen collected, types of specimen storage, and storage location of specimen aliquot or tissue vial or block.

Task 7. Develop an implementation test utilizing proposed software with a middle tier and internet interface for the Clinical Data Module (completed).
As previously reported, we have prepared much of the informatics infrastructure required to support the COE study. Infrastructure in place include: web server hardware, web service software, access security, data entry form templates, and referential integrity between database objects. We have refined an Access database to track information that is collected on our Patient Level Clinical Diagnosis Form. This form provides appropriate information to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. It also captures receptor status information, such as estrogen or progesterone positivity/negativity, which will be used to select specimens for the different specimen sets. This database acts as our "clinical module" and is linked to SIM, our primary data management system, which in turn is linked to the STS and SpecimenDB (see task 8 below for more detail.)

Figure 1: Screen shot of Patient Level Clinical Diagnosis data entry in Access database

Web based screens in SIM for questionnaire data entry and patient tracking have been developed and are currently in use by the two COE recruitment sites in Seattle and Los Angeles. Routines for data validation with each submission of data to the server have been implemented. Every value entered is checked for validity. Any outliers are returned to the data entry specialist for verification before the data are committed to the database. In addition, attempts to re-enter data that have previously been collected, are preempted via referential integrity.

This year we have added new features to the shared SIM database that allow us to generate status reports and documents for participant mailings, and to track participant contact for the study at FHCRC. Study staff can search for reports or documents by study or name. Current reports or participant documents with updated information can be created by clicking a link in the "request" column below. Static reports and forms can also be accessed through this portal.

TOR SIM System

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Available Records

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REPORT NAME	FOR	REQUEST	AVAILABLE	STATUS
Test COE Surgical - To Do List	Carole	Create	10/04/2007	
Test COE Surgical - To Do List	Carole	Create	10/04/2007	
Test COE Surgical Baseline Questionnaire Reminder Call - Call Log		Create		
Test COE Surgical Baseline Questionnaire Reminder Mailing - Labels		Create		
Test COE Surgical Baseline Questionnaire Reminder Mailing - Letter		Create		
Test COE Surgical Baseline Questionnaire Reminder Mailing - Patient List		Create		
Test COE Surgical End of Study Thank You Mailing - Labels		Create		
Test COE Surgical End of Study Thank You Mailing - Letter		Create		
Test COE Surgical End of Study Thank You Mailing - Patient List		Create		
Test COE Surgical Enrollment Appointment - Baseline Questionnaire		Static	View	
Test COE Surgical Enrollment Appointment - Breast Blood Collection Form		Static	View	
Test COE Surgical Enrollment Appointment - Breast PBMC Specimen Tracking Form		Static	View	
Test COE Surgical Enrollment Appointment - Breast Tissue Collection Form		Static	View	
Test COE Surgical Enrollment Appointment - Consent Form		Static	View	
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Test COE Surgical Enrollment Appointment - Health Status Questionnaire		Static	View	
Test COE Surgical Enrollment Appointment - Medical Records Release Form		Static	View	
Test COE Surgical First Follow-Up Appointment Confirmation Mailing - Confirmation Letter	Shelly	Create	10/02/2007	Confirm
Test COE Surgical First Follow-Up Appointment Confirmation Mailing - Health Status Update Questionnai	Shelly	Create	10/02/2007	Confirm
Test COE Surgical First Follow-Up Appointment Confirmation Mailing - Labels	Shelly	Create	10/02/2007	Confirm
Test COE Surgical First Follow-Up Appointment Confirmation Mailing - Patient List	Shelly	Create	10/02/2007	Confirm
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Test COE Surgical First Follow-up Appointment Reminder Call - Patient List	Shelly	Create	10/02/2007	Confirm
Test COE Surgical First Follow-up Appointment Reminder Mailing - Labels	Shelly	Create	10/02/2007	Confirm
Test COE Surgical First Follow-up Appointment Reminder Mailing - Letter	Shelly	Create	10/02/2007	Confirm

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Figure 2: New reporting screen with mail merge capabilities

Task 8. Develop breast specimen tracking database to replicate and enhance the current system's functionality adjusting per information gained in the implementation test (completed).

As previously reported Staff Scientist Dr. Michèl Schummer developed SpecimenDB, a FileMaker database for information that is generated from our specimens, such as experimental and specimen processing results. SpecimenDB also serves as a front-end to COE databases SIM, STS and the Access database tracking our Patient Level Clinical Diagnosis Form. The interface provides a unified look across all components and is thus easy to navigate. Each field can be searched without knowledge of the underlying structure. Summary reports can be generated from any view as Excel or PDF documents. SpecimenDB is client- and web-based, the latter allowing for collaboration across sites. Although the back-end consists of several databases, the user sees just three major areas: Specimens, Patients and Results.

The Specimens area holds data about the processing of the specimens, such as RNA extraction (Figure 3a.) This allows for technicians to enter information pertaining to specimen processing. Having this information in a central location will prevent us from distributing a specimen that was previously known to yield poor RNA or protein. The Specimens area also has a view that lists multiple specimens in rows which allows for intuitive searches and the generation of summary reports (Figure 3b.)

Figure 3a: Specimen extracts view

Figure 3b: Specimen list view based on patients selected in the patient list view

The Patients area holds patient-related information that has been stripped of identifying information, including the pathology reports, both abstracted and a scanned copy. Similar to the specimen area, it is possible to toggle between views that list detailed information about a single or multiple patients. In list view, it is further possible to toggle between patients and their specimens, allowing for simultaneous querying of patient and specimen information (Figure 3c.)

Figure 3c: Patient list view

The Report area is designed to contain experimental data obtained from the specimens in our repository. We have designed a database module (written in FoxPro) that keeps track of our serum and plasma marker measurement workflow, including the results. Although optimized to work with our laboratory, this module can also accommodate results data generated in other laboratories. We are currently expanding SpecimenDB capabilities to link to these results. This will allow us to perform queries across patients, specimens and results simultaneously in an extremely user-friendly manner. The new, integrated view will look very similar to the current view (Figure 3d.)

Specimen 100018 / Patient 127

GroupID	UPN	SpecimenID	Exp.ID	Date	Experiment Description	Analyte	Raw Data	Unit	Interpolated Data	Unit	Lab ID	Sample Description	Data Entry Date
142	233	201055	698	2000-05-21	Realtime PCR (SYBR	KRT8			0.26	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
135	226	201102	699	2000-05-21	Realtime PCR (SYBR	KRT8			0.00	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
148	239	201171	700	2000-05-21	Realtime PCR (SYBR	KRT8			0.03	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
144	235	201185	701	2000-05-21	Realtime PCR (SYBR	KRT8			0.01	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
141	232	201310	702	2000-05-21	Realtime PCR (SYBR	KRT8			0.01	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
189	280	201324	703	2000-05-21	Realtime PCR (SYBR	KRT8			0.24	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
215	306	201396	704	2000-05-21	Realtime PCR (SYBR	KRT8			0.16	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
226	316	201530	705	2000-05-21	Realtime PCR (SYBR	KRT8			0.13	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
230	320	201590	706	2000-05-21	Realtime PCR (SYBR	KRT8			0.07	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
231	321	201611	707	2000-05-21	Realtime PCR (SYBR	KRT8			0.02	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
237	239	201624	708	2000-05-21	Realtime PCR (SYBR	KRT8			0.33	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
248	337	201787	709	2000-05-21	Realtime PCR (SYBR	KRT8			0.01	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
253	342	201822	710	2000-05-21	Realtime PCR (SYBR	KRT8			0.17	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
256	345	201844	711	2000-05-21	Realtime PCR (SYBR	KRT8			0.20	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
257	346	201865	712	2000-05-21	Realtime PCR (SYBR	KRT8			0.04	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
270	359	202028	713	2000-05-21	Realtime PCR (SYBR	KRT8			0.01	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
277	366	202131	714	2000-05-21	Realtime PCR (SYBR	KRT8			0.20	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
295	384	202156	715	2000-05-21	Realtime PCR (SYBR	KRT8			0.11	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
296	385	202192	716	2000-05-21	Realtime PCR (SYBR	KRT8			0.01	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
308	397	202308	717	2000-05-21	Realtime PCR (SYBR	KRT8			0.09	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
304	393	202322	718	2000-05-21	Realtime PCR (SYBR	KRT8			0.34	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
235	325	202520	719	2000-05-21	Realtime PCR (SYBR	KRT8			0.05	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
275	364	202629	720	2000-05-21	Realtime PCR (SYBR	KRT8			0.04	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10
305	394	202824	721	2000-05-21	Realtime PCR (SYBR	KRT8			0.00	Relat	Schu	ForwardPrimer: taaggatgccaacgccaagtt	2006-07-10

Figure 3d: Results view for specimens assayed for KRT8 expression

Task 9. Develop collaborative web site

Task 9a: Develop site to support real-time discussion and information sharing among investigators (Completed). Investigators and study staff utilize the CPAS website, created by Dr. Martin McIntosh and his Computational Proteomics Laboratory group at the Fred Hutchinson Center. CPAS is an open-source science portal offering web-based bioinformatics and collaboration tools to help scientists store, analyze and share data from high-throughput experiments and clinical trials. CPAS is available as free, installable software, with source code. This work is being done as part of a project funded by an NCI subcontract (23XS144A).

Study investigators and staff continue to use CPAS to support real-time communication and information sharing among FHCRC staff, COE investigators and their respective staff. A username and password are required to access information on this site. The content on CPAS is organized hierarchically into projects and subfolders, much like the file directories on your computer; therefore, users find it easy to navigate through and use. The left side of each CPAS web page displays this tree-like structure as shown below.

Figure 4: Screen shot of project management page on CPAS

In addition to CPAS, we created a second website to function as a study reference to outside researchers and the general public. This website went live earlier this year and can be viewed at www.breastcancerbiomarkers.org.   The website consists of four main sections: a Homepage, Research Overview, Advocacy, and Community Events. There is also a special link to our internal CPAS site accessible only to project investigators and staff.
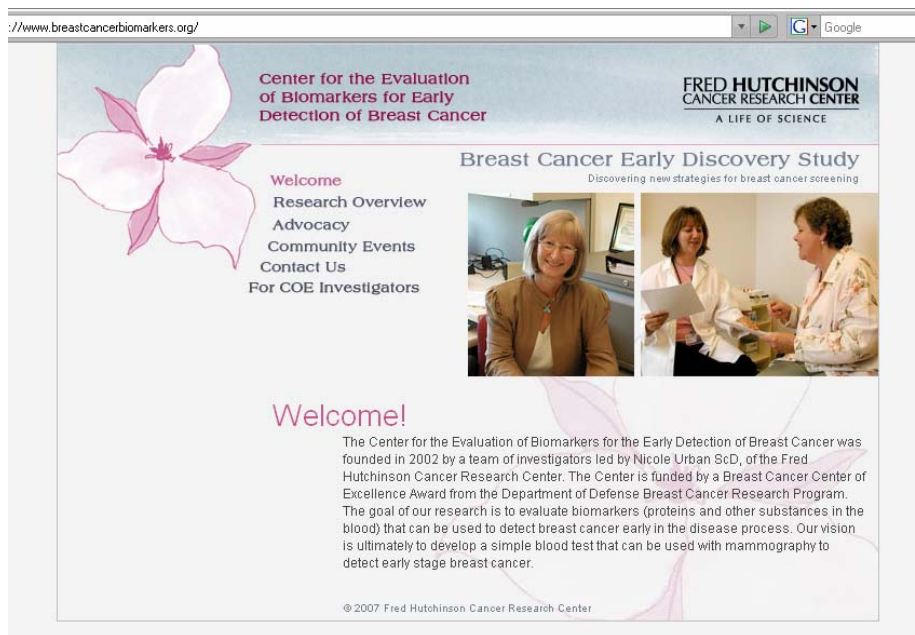
Figure 5. External website homepage.

The Research Overview section contains pages dedicated to the following areas of the study: a) an overview of our research and our research team, b) the COE study population, c) our methods for specimen collection, d) information on the biomarker evaluation and marker panel development, e) the clinical relevance of a marker panel, f) our existing resources, and g) additional resources needed (e.g. candidate biomarkers). The Advocacy page provides information on our breast advocacy program and the role of the patient advocate in our work. The Community Events page lists upcoming events that focus on patient advocacy, breast cancer awareness, health education, and wellness. The website is maintained and updated on a regular basis by study staff.

Task 9b: Develop extensions that will give investigators ability to query specimen tracking system and download summary reports (Completed). In spite of its name, SpecimenDB (explained in detail under Task 8) tracks both specimen and patient related (clinical) information. Its unification of several databases allows investigator-generated queries. For example, a user can select patients that match certain clinical criteria and click on the "toggle specimens" button. Available specimens matching the criteria will be shown. The user can then search for subsets of these specimens, such as available serum volume. Queries can be performed in increments, which will allow the investigator to review the data between steps. Multiple AND or OR statements can be applied without knowledge of the underlying database structure. Once a subset of records has been identified, a summary report can be generated through pre-configured templates, or ad-hoc, through user-selection. To facilitate this process, field names are the same in the user interface as in the underlying database. In addition, the COE CPAS site is linked to the study's data management system; therefore, investigators are able to access and view data reports as if they were in the SIM system.

Task 9c: Develop web pages for each investigator that are linked to collaborative site (Completed). We have developed folders on CPAS for each laboratory based investigator. Each investigator will be able to design their own folder and create subfolders suiting their specific needs; however, we will request that investigators use their folders to upload all laboratory results and to view marker results.

We have also developed folders to support investigator specific meetings and collaborative activities, such as the quarterly investigator calls and the developing Specimen Review Committee. In addition, we have created a folder that is open to the

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public to support the upcoming COE investigator meetings such as our annual workshop on November 2, 2007.
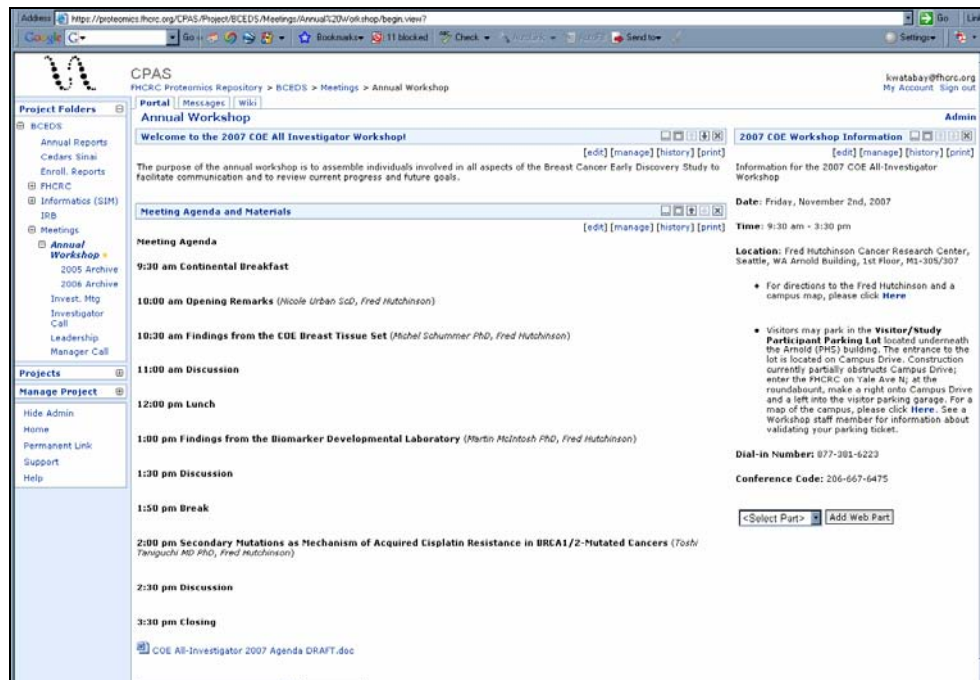

Figure 6. Screenshot of Annual Workshop homepage on CPAS.

Task 10: Prepare and Analyze Breast Mini-Triage Set (Formerly called ARTS)

Task 10a: Provide blinded samples from a set of 80 women to laboratory investigators (months 49-54). Investigators are in the process of selecting specimens for the first set, the Breast Mini-Triage Set (BMTS) that will be provided to study laboratory investigators to determine the preliminary usefulness of new markers. This set will consist of approximately 40 cases and 40 controls, depending on availability of suitable specimens in the repository. Cases and controls will be matched on the following variables: age, menopausal status, race, HRT use, risk status, and length of time specimens have been in storage. During the next year we plan to work with collaborating investigators to evaluate markers in the BMTS that have performed well in preliminary tests using unblinded COE specimens. Dr. Victor Levenson of Northwestern University has used a preliminary set of unblinded COE specimens to identify a panel of methylation markers. In our TOR Laboratory we are evaluating a S100A7 marker identified by Dr. Kornelia Polyàk of Dana Farber Cancer Institute. Dr. Samir Hanash at the Fred Hutchinson Cancer Research Center has identified candidate markers derived from mouse breast cancer IPAS experiments; he will work with other COE investigators to develop assays and validate these candidates, using plasma from newly diagnosed human breast cancer patients and matched controls from the COE repository. Other investigators who have expressed interest in our specimen sets include Dr. Sara Sukumar of Johns Hopkins, and Dr. Thea Tlsty of UCSF. In addition the BMTS will be made available to new collaborators that may have promising markers or discovery platforms through an RFA-type mechanism.

Tasks 10b and 10c: Statistical analysis of BMTS results and continued assay refinement (months 51-55). We anticipate conducting statistical analyses on preliminary assay results from the BMTS in 2008, and will provide results to laboratory scientists for continued assay refinement.

Tasks 11-13: Biomarker Panel Validation and Evaluation (months 55-72)
Once statistical analyses of the BMTS results are complete, investigators will select specimens for the Panel Development and Validation Sets. To help us identify a marker panel with a high level of sensitivity and specificity, we will continue to seek additional collaborators who may have promising markers available for evaluation.

Key Research Accomplishments

- Study Accrual – on target to meet most of our accrual goals through enrollment year 3 (October 1, 2004 through September 30, 2007.)

	Cumulative Accrual Goals through enrollment year 3	TOTAL Actual Accrual
Mammography Cohort -- High/Elevated Risk	525	558
Mammography Cohort – Average Risk	175	118
Mammography Cohort – Biopsy	300	13
Subtotal: Mammography Cohort	*1000*	*689*
Avon Study (P5OCA83636) participants whose specimens could be included with the biopsy samples for validation. (see task 2b)		*139*
SMC Surgical Cohort: Blood and Tissue	125	100
SMC Surgical Cohort: Blood Only	200	222
Subtotal: Surgical Cohort	*325*	*322*
Cedars Surgical Cohort: Blood and Tissue	150	86
Total	**1475**	**1097**

- COE Repository of donated blood and tissue specimens– we have continued contributing specimens to our established, well-characterized repository of serum, plasma, and fresh frozen tissue. Specimen data are linked to extensive epidemiological and clinical data including demographic information, information from GAIL model variables, pedigree, breast density, Bi-RADS assessment code and follow-up information from screening mammograms, ER/PR and Her2 status, staging and grade, and clinical follow-up for treatment and recurrence. We have also collected a number of matched pre- and post-diagnosis serum specimens from healthy controls that went on to develop breast cancer during the course of the study. During the remaining grant period stored specimens in the repository will be used by COE investigators to evaluate markers and conduct molecular profiling work.
- We have selected a preliminary set of blood samples from the repository for use as a Breast Discovery Set (BDS)- The BDS is provided to investigators who need to be unblinded to case/control status, histologic subtype, stage, and perhaps additional marker information. This set is currently being used by COE investigators and collaborators to evaluate markers and conduct the molecular profiling work described in project Aim 3. This specimen set may also be made available to outside investigators who have promising biomarkers or discovery platforms through an RFA mechanism. In our Translational and Outcomes Research (TOR) Laboratory we have identified a list of 14 promising candidate markers for discovery. During the next funding period the TOR Laboratory will work with our collaborators to develop assays for these candidates, and those that perform well in preliminary analyses will go on to be evaluated in the BDS.
- Serum collection conditions may influence laboratory results for some biomarkers - The use of blood-based biomarkers holds promise for improving outcomes for cancer

through early detection, however since cases often provide blood samples during surgery and controls often provide samples under non-surgical conditions, there may be an inherent bias associated with biomarker discovery and validation related to the conditions of the specimen collection. We have recently submitted a paper for publication that assesses whether the conditions of specimen collection influenced the levels of three previously identified serum biomarkers for ovarian cancer (CA125, prolactin and MIF.) Serum concentrations were analyzed in healthy women participating in the COE mammography cohort, women with ovarian cancer undergoing gynecologic surgery, women undergoing surgery for benign ovary pathology, and women undergoing surgery with pathologically normal ovaries. For women undergoing surgery serum specimens were collected either in the clinic 1 to 39 days prior to surgery, on the day of surgery after anesthesia was administered but prior to the start of surgery, or both. Unlike CA125 and MIF, no difference was found in prolactin levels between case and control groups after accounting for the conditions of sample collection. This suggests that for some markers, the conditions of the collection may influence laboratory results. Although adjusting for covariates is commonplace in epidemiological studies, this concept is relatively new in the field of biomarker diagnostics. The results from this study may help investigators to identify and account for potential biases due to specimen collection conditions. Thorpe, JD, Duan X, Forrest R, Lowe K, Brown L, Segal E, Nelson B, Anderson G, McIntosh M, Urban N Effects of Blood Collection Conditions on Ovarian Cancer Serum Markers. Submitted to *PLoS:ONE*, October 2007

Reportable Outcomes

COE investigator Dr. Martin McIntosh is currently collaborating with Dr. Paul Lampe of the Fred Hutchinson Cancer Research Center on a Biomarker Development Laboratory in the Early Detection Research Network of the National Cancer Institute Award (U01 CA111273, 09/01/2005 – 07/31/2010). The goal of this work is to identify biomarkers that, when used together, can diagnose breast cancer early when therapies are most effective. Biomarker discovery is based on using antibody sub libraries selected from tissue proximal fluids, and then evaluating their performance in serum or plasma using antibody arrays. This work will address a major barrio to the translation of serum biomarker discoveries: the inability to evaluate putative biomarkers in high throughput validation studies. Specimens from the COE repository are being used to support the discovery and validation work in this project. Currently one publication has resulted from this research: Loch, C. M., Ramirez, A. B., Liu, Y., Sather, C. L., Delrow, J.J., Garvik, B., Scholler, N., Urban, N., McIntosh, M. W. and Lampe, P. D. Use of High Density Antibody Arrays to Validate and Discover Cancer Serum Biomarkers. *Molecular Oncology.* In press.

During the past funding period two additional projects have produced papers acknowledging the support of the COE award: Urban ND, Longton GM, Crowe AD, Drucker MJ, Lehman CD, Peacock S, Lowe KA, Zeliadt SB, Gaul MA. Computer-Assisted Mammography Feedback Program (CAMFP): An Electronic Tool for Continuing Medical Education. *Academic Radiology.* 2007 Sep;14(9):1036-42 and Scholler N, Lowe K, Bergan L, Kampani A, Ng V, Forrest R, Thorpe J, Gross J, Garvik B, Drapkin R, Urban N. Use of yeast-secreted in vivo biotinylated recombinant antibodies (biobodies) in bead-based ELISA. Submitted to *Clinical Cancer Research*, October 2007.

COE collaborator Dr. Samir Hanash of the Fred Hutchinson Cancer Research Center has recently received funding for a new project that will utilize specimens from the COE repository, "Alliance of Glycobiologists for Detection of Cancer and Cancer Risk" (U01 CA128427.) The study involves implementation of a new paradigm in the use of glycan

biomarkers for early detection of cancer. Specific aim 1 focuses on the analysis of glycans and glycoproteins in plasma to identify differences in plasma between newly diagnosed breast cancer subjects and controls. Specific aim 2 focuses on the analysis of breast cancer tissue obtained at the time of surgery to identify glycan and glycoprotein differences between tumor containing and tumor free tissue. Specific aim 3 will focus on the development of a high throughput and sensitive glycan assay platform (GAP) which will be used to pre-validate markers in a large sample set to facilitate future clinical studies.

As encouraged at the 2006 COE workshop in Arlington, Virginia, resources are now being devoted to conduct discovery work in both serum and breast tissue, since there are not enough candidate markers currently ready or available for evaluation. This year COE investigator Dr. Michèl Schummer began a discovery project using RNA extracted from COE cases and controls to look at expression in approximately 100 genes that have been identified in the literature or by our collaborators as being potentially involved in the development of breast cancer. A novel aspect of this project is that it will look at expression in normal breast tissue collected from healthy participants undergoing reduction mammoplasty and other breast plastic surgery procedures at Cedars-Sinai, as well as tissue from women with cancer and benign disease. All specimens will first be histologically characterized and then undergo RNA extraction. Dr. Schummer will select a subset of these specimens to be used in real time PCR experiments to evaluate gene expression. Dr. Schummer plans to present the preliminary results of this work during the November 2nd annual COE workshop in Seattle.

As mentioned above, investigators and study staff use the CPAS website, created by Dr. Martin McIntosh and his Computational Proteomics Laboratory group at the Fred Hutchinson Center to support real time communication and project management issues associated with this study. CPAS is an open-source science portal offering web-based bioinformatics and collaboration tools to help scientists store, analyze and share data from high-throughput experiments and clinical trials. CPAS is available as free, installable software, with source code, and can be downloaded at: http://cpas.fhcrc.org.

Conclusions

No research conclusions are available at this time.

Appendices

Appendix A   2006 All-Investigator Workshop Meeting Agenda
Appendix B   Surgical Cohort Enrollment Reports
Appendix C   End of Study Questionnaire Supplement

CENTER OF EXCELLENCE ALL-INVESTIGATOR WORKSHOP

November 3, 2006

Center for the Evaluation of Biomarkers for Early Detection of Breast Cancer
Fred Hutchinson Cancer Research Center, Seattle, WA
Day Campus, Arnold Building 1st Floor M1-A303/305/307   *Questions? Please call 206-667-4238*

8:30 am   CONTINENTAL BREAKFAST

9:00 am   **Opening Remarks**
Nicole Urban, ScD   *Fred Hutchinson Cancer Research Center*

9:30 am   **Clinical Usefulness of Expression Arrays for Adjuvant Therapy Decision-Making**
Scott Karlan, MD   *Cedars-Sinai Medical Center*

10:00 am   **New Tumor Antigen Discovery-From Mice to Human**
Hailing Lu, PhD   *University of Washington*

10:30 am   **Development of a New Discovery Platform Based on Recombinant Antibodies to Identify Candidate Biomarkers of Breast Cancer**
Nathalie Scholler, MD, PhD   *Fred Hutchinson Cancer Research Center*

11:00 am   **Discussion**

12:00 pm   LUNCH

1:00 pm   **Innovative Strategies for Cancer Biomarker Discovery**
Samir Hanash, MD, PhD   *Fred Hutchinson Cancer Research Center*

1:45 pm   **Discussion: Mammography**
Mariann Drucker, MD and Justin Smith, MD   *Swedish Medical Center, Seattle Radiologists, and Inland Imaging*

2:30 pm   BREAK

2:45 pm   **Principles of and Indications for Breast MR**
Bruce Porter, MD   *First Hill Diagnostic Imaging and the University of Washington*

3:15 pm   **Discussion**

4:45 pm   CLOSING

	With Baseline			Without Baseline			Grand
	SMC	Cedar	Total	SMC	Cedar	Total	**Totals**
Enrollments With Blood and/or Tissue Collections							
Breast Cancer Cases							
Invasive	206	24	230	36	32	68	**298**
In Situ	40	8	48	6	12	18	**66**
Atypia	4	7	11	0	4	4	**15**
Subtotal: Cases	250	39	289	42	48	90	**379**
Surgical Controls							
Benign	8	19	27	2	24	26	**53**
Normal							
NED	0	1	1	0	0	0	**1**
Subtotal: Controls	8	20	28	2	24	26	**54**
Others							
Surgery Pending or no surgery	9	6	15	10	15	25	**40**
Diagnosis Pending	12	0	12	2	0	2	**14**
Subtotal: Others	21	6	27	12	15	27	**54**
Total Enrollments with Collections	279	65	344	56	87	143	**487**
Enrollments with no Collections	2	0	2	1	0	1	**3**
Percent Collected	99%	100%	99%	98%	100%	99%	**99%**
Surgical Cases with Collections							
Pre-Surgical Blood Only	21	1	22	5	2	7	**29**
Surgical Blood Only	47	0	47	11	0	11	**58**
Tissue Only	2	6	8	1	19	20	**28**
Pre-Surgical and Surgical Blood Only	100	0	100	10	0	10	**110**
Pre-Surgical and Tissue Only	3	31	34	2	27	29	**63**
Surgical Blood and Tissue Only	29	1	30	5	0	5	**35**
Pre-Surgical, Surgical Blood and Tissue	48	0	48	8	0	8	**56**
Those with Tissue subtotal	82	38	120	16	46	62	**182**
Surgical Controls with Collections							
Pre-Surgical Blood Only	3	2	5	2	1	3	**8**
Surgical Blood Only	3	0	3	0	1	1	**4**
Tissue Only	0	3	3	0	12	12	**15**
Pre-Surgical and Surgical Blood Only	1	0	1	0	0	0	**1**
Pre-Surgical and Tissue Only	**0**	**15**	**15**	**0**	**9**	**9**	**24**
Surgical Blood and Tissue Only	0	0	0	0	1	1	**1**
Pre-Surgical, Surgical Blood and Tissue	1	0	1	0	0	0	**1**
Those with Tissue subtotal	1	18	19	0	22	22	**41**

	With Baseline			Without Baseline			Grand
	SMC	Cedar	Total	SMC	Cedar	Total	Totals
Other (Pending) with Collections							
Pre-Surgical Blood Only	2	3	5	0	1	1	**6**
Surgical Blood Only	6	0	6	2	0	2	**8**
Tissue Only	0	0	0	1	9	10	**10**
Pre-Surgical and Surgical Blood Only	4	0	4	0	0	0	**4**
Pre-Surgical and Tissue Only	0	3	3	0	4	4	**7**
Surgical Blood and Tissue Only	2	0	2	0	1	1	**3**
Pre-Surgical, Surgical Blood and Tissue							
Those with Tissue subtotal	2	3	5	1	14	15	**20**
Those with Tissue Grand Total	85	59	144	17	82	99	**243**
Patients with Blood only Collected	187	6	193	30	5	35	**228**
Goal for years 1-3 (Oct 1, 2004 - Sep 30 2007)	200	0	200	0	0	0	**200**
Cumulative Study Goal (all 4 years)	300	0	300	0	0	0	**300**
Patients with Blood and Tissue Collected	83	50	133	15	42	57	**190**
Goal for years 1-3 (Oct 1, 2004 - Sep 30 2007)	125	150	275	0	0	0	**275**
Cumulative Study Goal (all 4 years)	175	200	375	0	0	0	**375**

		Previous Jul 04 - Dec 06	1st qtr 07 Jan 07 - Mar 07	2nd qtr 07 Apr 07 - Jun 07	3rd qtr 07 Jul 07 - Sep 07	Current Qtr Oct 07 - Dec 07	Current Totals Jul 04 - Dec 07
FHCRC	**Breast Cancer Cases**						
	Invasive						
	Bilateral Mastectomy	9	0	0	0	22	31
	Mastectomy	16	2	1	0	79	98
	Lumpectomy	11	0	3	1	104	119
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Invasive	36	2	4	1	205	248
	In Situ						
	Bilateral Mastectomy	0	0	0	0	7	7
	Mastectomy	4	0	0	0	17	21
	Lumpectomy	4	0	0	0	17	21
	Reduction Mammoplasty	0	0	0	0	0	0
	Total In Situ	8	0	0	0	41	49
	Atypia						
	Bilateral Mastectomy	0	0	0	0	1	1
	Mastectomy	0	0	0	0	0	0
	Lumpectomy	0	0	0	0	3	3
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Atypia	0	0	0	0	4	4
	Total Cases	44	2	4	1	250	301
	Surgical Controls						
	Benign						
	Bilateral Mastectomy	0	0	0	0	3	3
	Mastectomy	0	0	0	0	2	2
	Lumpectomy	1	0	1	0	4	6
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Benign	1	0	1	0	9	11
	Normal						
	Bilateral Mastectomy	0	0	0	0	0	0
	Mastectomy	0	0	0	0	0	0
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Normal	0	0	0	0	0	0
	NED						
	Bilateral Mastectomy	0	0	0	0	0	0
	Mastectomy	0	0	0	0	0	0
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	0	0	0	0	0	0
	Total NED	0	0	0	0	0	0
	Total Controls	1	0	1	0	9	11
	Case Status Pending	8	1		2	26	37
	Total FHCRC	53	3	5	3	285	349

Cedars	**Breast Cancer Cases**						
	Invasive						
	Bilateral Mastectomy	13	4	0	1	0	18
	Mastectomy	9	4	6	1	1	21
	Lumpectomy	8	0	2	2	3	15
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Invasive	30	8	8	4	4	54
	In Situ						
	Bilateral Mastectomy	7	3	1	0	1	12
	Mastectomy	5	2	0	0	0	7
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	0	0	0	0	0	0
	Total In Situ	12	5	1	0	1	19
	Atypia						
	Bilateral Mastectomy	5	1	0	0	0	6
	Mastectomy	3	0	0	0	0	3
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	1	0	0	0	0	1
	Total Atypia	9	1	0	0	0	10
	Total Cases	51	14	9	4	6	84
	Surgical Controls						
	Benign						
	Bilateral Mastectomy	7	7	2	1	0	17
	Mastectomy	2	3	0	1	1	7
	Lumpectomy	2	0	0	0	0	2
	Reduction Mammoplasty	6	0	1	2	1	10
	Total Benign	17	10	3	4	2	36
	Normal						
	Bilateral Mastectomy	0	0	0	0	0	0
	Mastectomy	0	0	0	0	0	0
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	0	0	0	0	0	0
	Total Normal	0	0	0	0	0	0
	NED						
	Bilateral Mastectomy	0	0	0	0	0	0
	Mastectomy	0	0	0	0	0	0
	Lumpectomy	0	0	0	0	0	0
	Reduction Mammoplasty	1	0	0	0	0	1
	Total NED	1	0	0	0	0	1
	Total Controls	18	10	3	6	3	40
	Case Status Pending	10		1	2	11	24
	Total Cedars	79	24	13	12	20	148

Overall   **Breast Cancer Cases**

Invasive

Bilateral Mastectomy	22	4	0	1	22	49
Mastectomy	25	6	7	1	80	119
Lumpectomy	19	0	5	3	107	134
Reduction Mammoplasty	0	0	0	0	0	0
Total Invasive	66	10	12	5	209	302

In Situ

Bilateral Mastectomy	7	3	1	0	8	19
Mastectomy	9	2	0	0	17	28
Lumpectomy	4	0	0	0	17	21
Reduction Mammoplasty	0	0	0	0	0	0
Total In Situ	20	5	1	0	42	68

Atypia

Bilateral Mastectomy	5	1	0	0	1	7
Mastectomy	3	0	0	0	0	3
Lumpectomy	0	0	0	0	3	3
Reduction Mammoplasty	1	0	0	0	0	1
Total Atypia	9	1	0	0	4	14
Total Cases	95	16	13	5	256	385

Surgical Controls

Benign

Bilateral Mastectomy	7	7	2	1	3	20
Mastectomy	2	3	0	1	3	9
Lumpectomy	3	0	1	0	4	8
Reduction Mammoplasty	6	0	1	2	1	10
Total Benign	18	10	4	4	11	47

Normal

Bilateral Mastectomy	0	0	0	0	0	0
Mastectomy	0	0	0	0	0	0
Lumpectomy	0	0	0	0	0	0
Reduction Mammoplasty	0	0	0	0	0	0
Total Normal	0	0	0	0	0	0

NED

Bilateral Mastectomy	0	0	0	0	0	0
Mastectomy	0	0	0	0	0	0
Lumpectomy	0	0	0	0	0	0
Reduction Mammoplasty	1	0	0	0	0	1
Total NED	1	0	0	0	0	1
Total Controls	19	10	4	6	12	51

Case Status Pending	18	1	1	4	37	61
Total Overall	132	27	18	15	305	497

End Of Study Supplemental Questions

[03-05-2007]

The purpose of these questions is to collect updated family history information from you about things that may have changed since you first enrolled in this study. Completing these questions is <u>voluntary</u>, you are free to skip any of the questions you choose.

1. The following questions are about your FEMALE blood relatives (including half-sisters). For each relative, please complete each section.
For each disease that you answer "yes" to, please give your best estimate of age when diagnosed in the corresponding box. Please note in the last section "primary cancer" refers to where the cancer started, not where it spread. Please complete the table for **all** FEMALE blood relatives, both with or without cancer, whether alive or deceased.

Relatives	Is this relative a half-sibling? Yes	No	Is this individual still living? Yes	No	Current age or age at death	Ever had ovarian cancer? Yes	No	Age	Ever had breast cancer? Yes	No	Age	Ever had colorectal cancer? Yes	No	Age	Ever had any other primary cancer? Yes	No	Age	Cancer Type
₁Mother			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₂Mother's Mother			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₃Father's Mother			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₄Your Sister 1	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₄Your Sister 2	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₄Your Sister 3	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₅Mother's Sister 1	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₅Mother's Sister 2	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₅Mother's Sister 3	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₆Father's Sister 1	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₆Father's Sister 2	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₆Father's Sister 3	☐₁	☐₀	☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₇Your Daughter 1			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₇Your Daughter 2			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₇Your Daughter 3			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₈Your Niece 1			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₈Your Niece 2			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		
₈Your Niece 3			☐₁	☐₂		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		☐₁	☐₀		

2. The following questions are about your MALE relatives (including half-brothers). For each relative, please complete each section. For each disease that you answer "yes" to, please give your best estimate of age when diagnosed in the corresponding box. Please note in the last section "primary cancer" refers to where the cancer started, not where it spread. Please complete the table for **all** MALE blood relatives, both with or without cancer, whether alive or deceased.

Relatives	Is this relative a half-sibling?		Is this individual still living?		Current age or age at death	Ever had prostate cancer?			Ever had breast cancer?			Ever had colorectal cancer?			Ever had any other primary cancer?			
	Yes	No	Yes	No		Yes	No	Age	Yes	No	Age	Yes	No	Age	Yes	No	Age	Cancer Type
1 Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
2 Mother's Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
3 Father's Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
4 Your Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
4 Your Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
4 Your Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
5 Mother's Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
5 Mother's Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
5 Mother's Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
6 Father's Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
6 Father's Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
6 Father's Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
7 Your Son 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
7 Your Son 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
7 Your Son 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
8 Your Nephew 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
8 Your Nephew 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		
8 Your Nephew 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0		

Thank you for completing this questionnaire!